PATENT
CASE OC01121K

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF APPEALS AND INTERFERENCES

In re Application of:	
Sara L. Zaknoen	Examiner: Sheela Jitendra Huff
For Patent For: **Combination Therapy for Cancer**	Group Art Unit: 1642
Serial No.: **09/767,424**	Date: September 23, 2003
Filed: **January 22, 2001**	

Schering-Plough Corporation
Kenilworth, New Jersey 07033-0530

Mailstop: Appeal Brief – Patents
P.O. Box 1450
Commissioner for Patents
Alexandria, VA 22313-1450

BRIEF ON APPEAL

Sir:

I HEREBY CERTIFY THAT THIS CORRESPONDENCE IS BEING DEPOSITED WITH THE UNITED STATES POSTAL SERVICE AS FIRST CLASS MAIL IN AN ENVELOPE ADDRESSED TO COMMISSIONER FOR PATENTS, ALEXANDRIA, VA 22313-1450 ON

9/23
(DATE OF DEPOSIT)

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(REGISTERED REPRESENTATIVE)

(SIGNATURE AND DATE)

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I. REAL PARTY OF INTEREST

Schering Corporation, Galloping Hill Road, Kenilworth, New Jersey 07033, is the real party of interest for the above identified application.

II. RELATED APPEALS AND INTERFERENCES

There are no other appeals, and there are no interferences, for the above identified application which will directly affect or have a bearing on the Board's decision in this Appeal.

III. STATUS OF CLAIMS

A. Pending Claims:

Claims 1-22 are pending.

B. Appealed Claims

Claims 1-22 are being appealed.

IV. STATUS OF AMENDMENTS

No amendments have been made to the claims throughout the prosecution. A response to a rejection under 35 U.S.C. 103, was filed after the final rejection of April 23, 2003. In an Advisory Action dated July 25, 2003, the Examiner stated that the Continuation of Paper No. 5, does not place the application in condition for allowance because it reiterates applicant's previous arguments which were addressed in previous Office Actions.

V. SUMMARY OF THE INVENTION

This invention is directed to a method for treating a human patient afflicted with cancer, comprising administering therapeutically effective amounts of temozolomide and pegylated interferon alpha to such a patient. The temozolomide is administered to the patient in combination with the pegylated alpha interferon; that is, the temozolomide and pegylated interferon alpha doses are administered during the same treatment cycle.

VI. ISSUE

Are claims 1-22 unpatentable under 35 U.S.C. 103(a) as being unpatentable over the WO 97/12630 in view of Ragab, U.S. 6,346,524 and Kline U.S. 6,180,096 or WO 95/13090?

VII. GROUPING OF CLAIMS

The rejected claims stand or fall together.

VIII. THE ARGUMENT

The cited references do not teach, disclose or suggest Appellants' claimed invention.

Appellants' claimed invention is directed to a method for treating a human patient afflicted with cancer, comprising administering therapeutically effective amounts of temozolomide and pegylated interferon alpha to such a patient.

The combination of cited references does not suggest that temozolomide and pegylated interferon alpha can be used to treat cancer.

When making a rejection under 35 U.S.C. § 103, the Examiner has the burden of establishing a prima facie case of obviousness. **In re Fritch**, 23 U.S.P.Q.2d 1780, 1783 (Fed. Cir. 1992). The Examiner can satisfy this burden only by showing an objective teaching in the prior art, or knowledge generally available to one of ordinary skill in the art, which would lead an individual to combine the relevant teachings of the references [and/or the knowledge] in the manner suggested by the Examiner. Id.; **In re Fine**, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988).

Per **Graham v. John Deere Co.**, 383 U.S. 1, 148 USPQ 459 (1966) and MPEP § 2144, the criteria for a prima facie case of obviousness are:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence in the application indicating obviousness or nonobviousness.

The mere fact that the prior art could be modified does not make the modification obvious unless the prior art suggests the desirability of the modification. **In re Fritch**, 23 U.S.P.Q.2d at 1784; **In re Laskowski**, 10 U.S.P.Q.2d 1397, 1398 (Fed. Cir. 1989); **In re Gordon**, 221 U.S.P.Q. 1125, 1127 (Fed. Cir. 1984).

Because of the differences between the scope of the prior art and the claimed invention, per the first and second Graham factors, Appellant respectfully suggests that a prima facie case of obviousness cannot be established.

Appellant claims a method of treatment using therapeutically effective amounts of temozolomide in combination with **pegylated** interferon alpha. Therapeutically effective amounts temozolomide and pegylated interferon alpha are described on page 3, lines 16-27 and pages 6-7, lines 25, et al. **Pegylated** interferon alpha is described on page 4, lines 12-20 of the specification, as the polyethylene glycol modified conjugates of interferon alpha.

As previously stated, the Examiner has rejected claims 1-22 under 35 U.S.C. 103(a) as being unpatentable over the WO 97/12630 in view of Ragab, U.S. 6,346,524 and Kline U.S. 6,180,096 or WO 95/13090.

WO 97/12630 discloses the combination therapy of temozolomide and, interferon alpha, specifically interferon alpha 2b (see generally, Abstract, pages 4-5 of the specification and claims 1-21). However, as acknowledged by the Examiner, WO 97/12630, does not disclose the use of PEG_{12000}-interferon alpha 2b, the specific concentrations of PEG_{12000}-interferon alpha 2b and the formation of a kit. The Examiner references Kline and WO 95/13090 for their disclosure of PEG interferon alpha 2b (see generally, Abstract, for both references). However, there is no teaching or suggestion in Kline, WO 97/12630 or WO 95/13090 to combine **pegylated** interferon alpha 2b in combination with temozolomide to treat cancer. In fact, WO 97/12630 teaches away from the Appellant's invention by the fact that it uses **non-pegylated** alpha interferon rather than **pegylated** interferon alpha 2b. **Pegylated** interferon alpha and **non-pegylated** interferon alpha, as used in WO 97/12630 are distinct from one another. (See Appellant's specification, page 4, lines 12-23 and page 5, lines 1-27). Thus, WO 97/12630 cannot be relied upon to render the inventor's application obvious. Further, Ragab merely discloses the use of temozolomide **alone**, (see generally, Abstract, col. 2, lines 31-45 and claims 1-11 of Ragab) there is no teaching or suggestion of combination therapy with interferon alpha, let alone combination therapy with **pegylated** interferon alpha-2b. In addition, Appellant believes that one of ordinary skill in the art would not necessarily consider Ragab's mono therapy of temozolomide to treat cancer when practicing the combination temozolomide and **pegylated** interferon alpha-2b therapy described by the Appellant's invention, due to the additional presence of **pegylated** interferon alpha-2b in the Appellant's pending invention. Finally, neither Ragab, Kline, WO 97/12630 or WO 95/13090 contain any teaching or suggestion to combine any of

them in order to teach the Appellant's claimed invention, temozolomide in combination with **pegylated** interferon alpha 2b. Appellant respectfully suggests that per the first and second Graham factors, these differences in the scope and contents of the claimed invention from the cited art preclude a finding of obviousness. Therefore, because the prima facie elements obviousness have not been met, Appellant respectfully submits that the claimed invention is not obvious in light of Ragab, Kline, WO 97/12630 and WO 95/13090.

Appellant notes that the Examiner has pointed out in the office actions where dosing regimens and parameters were shown in the cited art. However, the fact that these regimens and parameters exist in the cited art does not necessarily mean there is an adequate basis for an obviousness rejection. As stated in **Rosemount, Inc. v. Beckmann Instruments, Inc.**, 727 F.2d. 1540, 1546, 221 U.S.P.Q. 1, 7 (Fed. Cir. 1984), a combination of prior art references may be patentable whether it be composed of elements all new, partly new, or all old. Appellant respectfully points out that it is NOT arguing these regimens and parameters for each component of the claimed invention are not found in the cited art. Rather, Appellant respectfully reiterates that none of the references **suggest or motivate** one of ordinary skill in the art to practice the claimed method of combination therapy with temozolomide and pegylated interferon. Appellant respectfully suggests that the claimed method has a synergistic advantage of utilizing this particular combination therapy at the claimed dosing levels and dosing schedule, to achieve higher response rates and/or reduced side effects in treating cancer patients. As support of this, Appellant again refers the to the detailed clinical study design as described in the specification from pages 8 to 23.

In addition to Appellant's argument that the references do not establish the prima facie case of obviousness, Appellant respectfully argues that the combination of references cited by the Examiner, WO 97/12630 in view of Ragab U.S. 6,346,524 and Kline U.S. 6,180,096 or WO 95/13090, do not contain the proper motivation to render the present invention obvious. Appellant maintains that none of the references, either alone or in combination, teaches Appellant's invention, a synergistic method of treatment using therapeutically effective amounts of temozolomide in combination with pegylated interferon alpha. It is maintained that the Examiner still fails to point out to the Appellant, where in Ragab, WO 97/12630,

Kline or WO 95/13090, a specific teaching to provide one of ordinary skill in the art the motivation to make obvious the claimed invention.

Appellant cites **In re Burt**, 356 F.2d 115, 121, 148 U.S.P.Q. 548, 553 (C.C.P.A. 1966), for the principal that "[s]ilence in a reference is hardly a proper substitute for an adequate disclosure of facts from which a conclusion of obviousness may justifiably follow." Appellant respectfully maintains the cited references are silent on the Appellant's claimed method of treatment, and that they do not provide one of ordinary skill in the art the motivation to combine them to render the claimed invention obvious. Furthermore, there is no sufficient guidance or teaching in any of the cited references that temozolomide and pegylated interferon-α can be synergistically combined to practice Appellant's invention.

As stated by the courts, motivation to combine references for an obviousness rejection cannot be derived from the Appellant's specification. As per **Joy Technologies v. Flakt, Inc.**, 820 F. Supp. 802 (D. Del. 1993), the court held that the standard for obviousness is whether the prior art would have suggested to one of ordinary skill in the art that a process should be carried out and would have a reasonable likelihood of success, viewed in light of the prior art. Both the suggestion and the expectation of success must be founded in the prior art, and not in light of the Appellant's disclosure (see also **In re Dow Chemical**, 837 F.2d 469 (Fed. Cir. 1988)). In **Grain Processing Corporation v. American Maize-Products**, 840 F.2d 902, 913 (Fed. Cir. 1988), the Federal Circuit stated that the question to ask to determine obviousness is whether there is something in the prior art as a whole to suggest the desirability, and thus the obviousness, of making the combination. The obviousness inquiry is NOT whether each element existed in the prior art, but whether the prior art made obvious the invention as a whole for which patentability is claimed. **Id. at 14**. (see also generally, **Rosemount, Inc. v. Beckmann Instruments, Inc.**, 727 F.2d. 1540, 1546, 221 U.S.P.Q. 1, 7 (Fed. Cir. 1984)).

Appellant respectfully suggests that the Examiner's objection is based on an "obvious to try" rationale that is to "vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result . . . where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it." **In re O'Farrell**, 853 F.2d 894, 903, 7 U.S.P.Q.2d 1637 1681 (Fed. Cir. 1988) (Citations omitted). Appellant respectfully suggests that the cited prior art

have been combined to the point where, rather generally, a method of combination therapy of pegylated interferon alpha and temozolomide has been arrived at. Unlike the cited prior art, Appellant provides precise dose levels of pegylated interferon alpha to be administered together with temozolomide. (See, specification, page 6, line 29 to page 7, line 12; and claims 3-5, 8-13, and 15-19). Further, Appellant's specification provides a detailed clinical study design for use with the claimed method, including parameters such as patient inclusion/exclusion criteria (pages 9-12), dose escalation/de-escalation schedules and dose limiting toxicity parameters (page 13), dose adjustment of temozolomide and peg-interferon alpha (page 19), and so forth throughout the remainder of the specification. Again, Appellant points out that the cited references are silent on these matters. None of the cited references suggest, let alone provide such detailed guidance to one of ordinary skill in the art to administer pegylated interferon alpha in combination with temozolomide.

Lastly, Appellant respectfully suggests that impermissible hindsight reconstruction has been applied in this case to render these claims obvious.

As stated by the Courts, "It is impermissible to use the claimed invention as an instruction manual or 'template' to piece together the teachings of the prior art so that the claimed invention is rendered obvious....'[o]ne cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention.'" **In re Fritch**, 23 U.S.P.Q.2d at 1784 (quoting **In re Fine**, 5 U.S.P.Q.2d at 1600). In **Uniroyal, Inc. v. Rudkin-Wiley Crop., 837 F.2d 1044, 1051, 5 U.S.P.Q.2d 1434, 1438** (Fed. Cir. 1988), the court held that when prior art references require selective combination by a court to render obvious a subsequent invention, there must be some reason for the combination other than the hindsight gleaned form the invention itself. Something in the prior art as a whole must suggest the desirability, and thus the obviousness, of making the combination. **Id.** (see also **In re Dow Chem. Co. v. American Cyanamid Co.**, 837 F.2d 469, 473 U.S.P.Q.2d 1529, 1531-32 (Fed. Cir. 1988) and **Grain Processing Corporation v. American Maize-Products**, 840 F.2d 902, 913 (Fed. Cir. 1988), where the Federal Circuit stated that care must be taken to avoid hindsight reconstruction.

Appellant claims a method of treatment using therapeutically effective amounts of temozolomide in combination with **pegylated** interferon alpha. Therapeutically effective amounts temozolomide and pegylated interferon alpha are described on

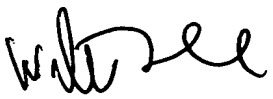
page 3, lines 16-27 and pages 6-7, lines 25, et al. **Pegylated** interferon alpha is described on page 4, lines 12-20 of the specification, as the polyethylene glycol modified conjugates of interferon alpha.

WO 97/12630 discloses the combination therapy of temozolomide and, interferon alpha, specifically interferon alpha 2b (see generally, Abstract, pages 4-5 of the specification and claims 1-21). Absent the teaching of pegylated interferon in WO 97/12630, the Examiner relies upon the references Kline and WO 95/13090 for their disclosure of PEG interferon alpha 2b (see generally, Abstract, for both references). , Finally, the Examiner cites Ragab and its use of temozolomide **alone**, (see generally, Abstract, col. 2, lines 31-45 and claims 1-11 of Ragab).

Appellant and the Examiner are both in agreement that, WO 97/12630, does not teach the use of pegylated interferon. However, Appellant respectfully suggests there is no suggestion or motivation from WO 97/12630, Kline, WO 95/13090 and Ragab to combine their teachings together to render the present invention, a method of treatment using therapeutically effective amounts of temozolomide in combination with pegylated interferon alpha, obvious under § 103. None of the references cited, either singly or in combination with each other, suggest the Appellant's claimed method of combination therapy with temozolomide and pegylated interferon. Furthermore, there is no teaching in any of the cited references that temozolomide and pegylated interferon-α can be synergistically combined. Appellant respectfully suggests that the only suggestion to combine the teachings of the cited references comes from the Appellant's specification itself. "There must be a reason or suggestion in the art for selecting the procedure used, other than the knowledge learned from Appellant's disclosure".

Therefore, the Board of Appeals is respectfully requested to reverse the rejection of Claims 1-22 and to allow these claims to issue.

Respectfully submitted,



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IX. APPENDIX

THE CLAIMS ON APPEAL

The claims on appeal are as follows:

1. A method for treating a human patient afflicted with cancer, comprising administering therapeutically effective amounts of temozolomide and pegylated interferon alpha to such a patient.

2. The method of claim 1, wherein the temozolomide is administered in repeated cycles, each cycle having a dosing period in which the temozolomide is administered daily at a dose of 50 to 400 mg/m^2/day for 5 to 25 days, followed by a rest period of 5 to 14 days in which temozolomide is not administered.

3. The method of claim 2, wherein the pegylated interferon alpha is pegylated interferon alpha-2b, and is administered in an amount of from 1.0 to 9.0 micrograms per kilogram administered once a week.

4. The method of claim 3, wherein the pegylated interferon alpha-2b is administered in an amount of from 1.0 to 6.5 micrograms per kilogram administered once a week.

5. The method of claim 4, wherein the pegylated interferon alpha-2b is PEG_{12000}-interferon alpha.

6. The method of claim 1, wherein the temozolomide is administered in repeated cycles, each cycle having a dosing period in which the temozolomide is administered daily at a dose of 100 to 200 mg/m^2/day for 5 to 25 days, followed by a rest period of 5 to 14 days in which temozolomide is not administered.

7. The method of claim 6, wherein the temozolomide dosing period is one or three weeks, and the temozolomide rest period is one week.

8. The method of claim 7, wherein the pegylated interferon alpha is pegylated interferon alpha-2b, and is administered in an amount of from 1.0 to 9.0 micrograms per kilogram administered once a week.

9. The method of claim 8, wherein the pegylated interferon alpha-2b is PEG_{12000}-interferon alpha.

10. The method of claim 9, wherein the pegylated interferon alpha-2b is administered in an amount of from 1.0 to 6.5 micrograms per kilogram administered once a week.

11. The method of claim 2, wherein the pegylated interferon alpha is pegylated interferon alpha-2a, and is administered in an amount of from 50 to 500 micrograms once a week.

12. The method of claim 11, wherein the pegylated interferon alpha-2a is administered in an amount of from 200 to 250 micrograms once a week.

13. The method of claim 1, wherein the temozolomide is administered in repeated cycles, each cycle having a dosing period in which the temozolomide is administered daily at a dose of 100 to 200 mg/m^2/day for 5 to 25 days, followed by a rest period of 5 to 14 days in which temozolomide is not administered, and wherein the pegylated interferon alpha is pegylated interferon alpha-2a, and the pegylated interferon alpha-2a is administered in an amount of from 50 to 500 micrograms once a week.

14. The method of claim 13, wherein the temozolomide dosing period is one or three weeks, and the temozolomide rest period is one week.

15. The method of claim 1, wherein the temozolomide is administered daily for six weeks at a dose of 50 to 200 mg/m^2/day, and wherein the pegylated interferon alpha is pegylated interferon alpha-2b, and the pegylated interferon alpha-2b is administered in an amount of from 1.0 to 9.0 micrograms per kilogram administered once a week.

16. The method of claim 15, wherein the pegylated interferon alpha-2b is PEG_{12000}-interferon alpha.

17. The method of claim 16, wherein the pegylated interferon alpha-2b, is administered in an amount of from 1.0 to 6.5 micrograms per kilogram administered once a week.

18. The method of claim 1, wherein the temozolomide is administered daily for six weeks at a dose of 50 to 200 mg/m^2/day, and wherein the pegylated interferon alpha is pegylated interferon alpha-2a, and the pegylated interferon alpha-2a is administered in an amount of from 50 to 500 micrograms once a week.

19. The method of claim 1, wherein the temozolomide and pegylated interferon alpha are administered in repeated 28 day cycles, each 28 day cycle having a dosing period wherein the temozolomide is administered on days 1-7 and 15-21 of said cycle at a daily dose of 75 to 150 mg/m^2/day and wherein the pegylated interferon alpha is adminstered on days 1, 8, 15 and 22 at a daily dosing of 1.5 to 6.0 micrograms per kg per day.

20. The method of claim 19, wherein the pegylated interferon alpha is pegylated interferon alpha-2b.

21. The method of claim 19, wherein the pegylated interferon alpha-2b is PEG_{12000}-interferon alpha.

22. A medical kit for treating a cancer patient is provided, comprising:

(a) a supply of temozolomide;

(b) a supply of pegylated interferon alpha; and

(c) printed instructions for administering temozolomide and pegylated interferon alpha to a cancer patient.